BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL.

Vol. III.—No. 27.] BALTIMORE, DECEMBER, 1892. [Price, 15 Cents.

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THE MICROCOCCUS LANCEOLATUS, WITH ESPECIAL REFERENCE TO THE ETIOLOGY OF ACUTE LOBAR PNEUMONIA.

By William H. Welch, M. D., *Professor of Pathology, Johns Hopkins University, and Pathologist to the Johns Hopkins Hospital.*

FIRST ARTICLE.

[These articles are based upon my lectures on the causation of acute lobar pneumonia, delivered at the Johns Hopkins Hospital in January, February and March, 1892, and upon the presidential address before the Medical and Chirurgical Faculty of the State of Maryland in April, 1892. As the publication of the articles has been delayed, the literature of the subject has been considered up to the present date. I have attempted to present in these papers a summary of the existing knowledge of the micrococcus lanceolatus, more especially in its relation to acute lobar pneumonia. My own observations of this organism relate to cultures and results of inoculation from about fifty cases of acute lobar pneumonia, from inflammatory exudates in several cases not associated with pneumonia, and also from the saliva or expectoration of persons not affected with pneumonia.]

Nomenclature.

Various names have been given to the species of bacterium which we believe to be the specific cause of acute lobar pneumonia, such as microbe septicémique du salive (Pasteur), micrococcus Pasteuri (Sternberg), coccus lanceolatus (Talamon), coccus of sputum septicæmia (A. Fraenkel), bacillus salivarius septicus (Biondi), bacillus septicus sputigenus (Flügge), diplococcus or diplo-bacillus or pneumo-coccus or pneumonia coccus of Fraenkel and Weichselbaum, diplococcus pneumoniæ (Weichselbaum), meningococcus (Foà and Bordoni-Uffreduzzi), glœococcus of Fraenkel (Klebs), micrococcus or diplococcus lanceolatus capsulatus (Foà and Bordoni-Uffreduzzi), streptococcus lanceolatus Pasteuri (Gamaleia), micrococcus pneumoniæ cruposæ (Sternberg). It is probable that the micrococcus pyogenes tenuis of Rosenbach is identical with the pneumonia coccus, as was first pointed out by Neumann.[1] It is evident that this organism has been sufficiently baptized. Of these names, micrococcus or diplococcus lanceolatus (with or without the additional epithet capsulatus), diplococcus pneumoniæ, and pneumonia or pneumo-coccus (Fraenkel-Weichselbaum) have gained the widest currency and will be used in this article. The objection to the names pneumo-coccus, micrococcus pneumoniæ cruposæ, diplococcus pneumoniæ is that they suggest an exclusive relationship of the organism to acute croupous pneumonia, whereas this same organism is concerned in the causation of epidemic cerebro-spinal meningitis and many other affections independent of pneumonia. Perhaps the name micrococcus lanceolatus is the least objectionable. Certainly one ought to hesitate before adding a new name to the already long and confusing list of synonyms.

History.

The micrococcus lanceolatus was discovered by Sternberg in September, 1880, by inoculation of rabbits with his own saliva. It was next found by Pasteur in December, 1880, by inoculating rabbits with the saliva of a child dead of hydrophobia. Pasteur's[2] observations were the first to be made public, being announced at the meeting of the Académie de Médecine in Paris on January 18, 1881. They gave rise to no less than

six communications to the same Academy in January, February and March, 1881.* Sternberg's[2] first publication on this subject appeared on April 30, 1881.

At this time there was no suspicion that this micrococcus of the saliva is concerned in the causation of lobar pneumonia. The bacteriological study of this disease, however, had already begun and went on for a time without any knowledge of the identity of the pneumonia coccus with the organism described by Sternberg and by Pasteur.

The idea that acute lobar pneumonia, at least in some of its forms, is an infectious disease, is centuries old, as has been shown especially by Hirsch,[4] but this idea gained wider acceptance and the arguments in its support were more fully and forcibly presented in the seventh decade of this century than ever before. Jürgensen,[5] Leichtenstern[6] and Flint[7] may be mentioned as strong and influential advocates of this view at this period. They brought together the leading anatomical, etiological and clinical facts at that time available to support the doctrine of the infectious nature of lobar pneumonia. The minds of many physicians, therefore, were prepared to accept the discovery of a specific micro-organism as the cause of the disease.

The attempts made by Klebs[8] as early as 1875 to cultivate bacteria from cases of croupous pneumonia were not by methods which could yield pure cultures. For this and other reasons his observations concerning his monas pulmonale can not be utilized.

There can be no doubt that in 1881 Eberth[9] and Koch,[10] and in 1882 Friedländer,[11] Leyden[12] and Günther,[13] demonstrated microscopically, in lungs affected with croupous pneumonia and in other parts of the body, the genuine diplococci of this disease, but they did not cultivate the organism. Leyden and Günther demonstrated the oval diplococci, surrounded with a capsule, according to Günther, in fluid withdrawn during life from the hepatized lung.

Manifestly little importance can be attached to such observations as those of Mátray[14] and of Ziehl[15] in 1883, who examined only microscopically pneumonic sputum, although their descriptions leave little doubt that they saw the pneumonia cocci.

It had been long known that pneumonic sputum may occasionally manifest toxic or infectious properties when inoculated into certain animals, but no specific significance could be attached to these observations, inasmuch as the sputum in other conditions and even in health may possess similar properties. In 1882 Griffini and Cambria[16] produced regularly septicæmia by inoculating rabbits and dogs subcutaneously with pneumonic sputum, and found that the disease could be transmitted by inoculating the blood of the animals dead of the infection.

In October of the same year Salvioli and Zäslein[17] claimed that cocci can be demonstrated regularly in the sputum, blood and blister-serum of patients affected with croupous pneumonia, and that fluid cultures from the blood or serum of cocci, sometimes mixed with rods, threads and spores, produce typical pneumonia and pleurisy when inoculated in rabbits and white rats. Very little weight can be attached to these experiments of Salvioli and Zäslein.

No little sensation was made by Friedländer's[18] publication in November, 1883, in which he described cultures of his pneumo-coccus. We now know that the so-called pneumococcus cultivated by Friedländer is an organism entirely distinct from the micrococcus lanceolatus, and is to be regarded as a bacillus. This pneumo-bacillus of Friedländer is probably in no way concerned in the causation of genuine acute

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*As the exact order in time of these first publications is rarely given correctly it may be well to state their precise sequence.

1. Bulletin de l'Acad. de Méd. Séance du 18 Jan. 1881. Raynaud et Lannelongue. Recherches expér. sur la transmission du virus rabique de l'homme au lapin. In the discussion following the reading of this paper Pasteur said that on Dec. 11, 1880, he had inoculated two rabbits with the saliva of a boy dead, 4 hours previously, from hydrophobia. In the blood of these rabbits, which died in 36 hours, he found a new species of bacterium, shaped like a figure of 8, surrounded with a gelatiniform envelope. The organism is virulent in broth cultures, in which it often forms chains. He expressed entire ignorance as to the relation of the organism to rabies, but emphasized the distinction between the new disease produced in rabbits and his vibrio septicæmia (now known as malignant œdema).

2. Ibid. Séance du 25 Jan. 1881. Pasteur. Note sur la maladie nouvelle provoquée par la salive d'un enfant mort de la rage. This communication was made by Pasteur in the names of himself, Chamberland, Roux and Thuillier. It contains a more detailed account of the new organism and the experiments mentioned at the previous meeting.

3. Ibid. Séance du 1 Fév. 1881. A prolonged discussion took place, especially between Pasteur and Colin, as to the propriety of regarding the "nouvelle maladie" of rabbits as septicæmia. The president of the Academy appointed a commission to report on this question.

4. Ibid. Séance du 8 Fév. 1881. Villemin, in the name of this commission, reports that the new disease is not septicæmia (that is, is not the affection then called septicæmia by French authors and which is produced by Pasteur's vibrion septique or the bacillus of malignant œdema).

5. Ibid. Séance du 22 Mars, 1881. In a letter to M. Parrot and presented by him to the Academy, Pasteur reports that he has now found the new bacterium in a second case of rabies (Feb. 24), in the mouths of three children dead of broncho-pneumonia and in the saliva of a healthy adult. He failed to find it in the saliva of three adults dead of common diseases. He says that it is evidently a common inhabitant of the mouth and that it has nothing to do with rabies. He believes that this organism will be found to have great significance in the etiology of disease.

6. Ibid. Séance du 29 Mars, 1881. Vulpian reports that he has also produced Pasteur's new disease by the inoculation of rabbits with the saliva of healthy persons. He made known these results in his lectures at the Faculty of Medicine on March 19 and 22, being assisted by Bochefontaine and Arthaud.

7. Sternberg, National Board of Health Bulletin, April 30, 1881, says that he has described this organism in a report (not then published) made to the National Board of Health in February, 1881. At the time of this publication Sternberg had become familiar with Pasteur's first communications on the "nouvelle maladie." While engaged in experiments intended to control Klebs and Tomassi-Crudeli's statements regarding the so-called bacillus malariæ, Sternberg found, in New Orleans, in September, 1880, that the subcutaneous inoculation of his own saliva in rabbits produced a fatal form of septicæmia with the micrococci under consideration in the blood. These first experiments were followed by others in the early part of 1881 in Philadelphia and Baltimore.

lobar pneumonia in man. Friedländer's method of cultivation in nutrient gelatine at ordinary temperatures precluded his obtaining the genuine pneumonia coccus. The historical importance of this publication of Friedländer is that he was the first to describe cultures obtained from croupous pneumonia by using Koch's solid nutritive media, that his pneumo-bacillus was widely accepted until the year 1886 as the specific cause of croupous pneumonia, and especially that his results gave an impetus to the bacteriological study of this disease by modern methods.

Inasmuch as Friedländer described his pneumonia organism as an oval coccus with a capsule, and as the micrococcus lanceolatus is an oval coccus with a capsule, there followed much confusion of these two organisms, which in fact can be readily differentiated by cultures and by inoculation of animals.

In contradistinction to these observations of Friedländer, those of Talamon,[19] made public before the Société Anatomique in Paris on November 30, 1883, unquestionably pertained to the genuine micrococcus lanceolatus. He recognized microscopically lanceolate cocci as the most common organisms in pneumonic sputum and exudate. This species of coccus was present in his bouillon cultures of pneumonic exudate at body temperature, and in two instances in pure cultures. Sixteen out of twenty rabbits inoculated in the chest with these cultures died of septicæmia combined often with fibrinous pleurisy and pericarditis, and the blood and exudates of these animals contained the same lanceolate cocci and gave origin to pure cultures which were again inoculated with the same results. Guinea-pigs and dogs were described as immune. Talamon found the characteristic cocci in fluid withdrawn during life by a hypodermic syringe from hepatized lung (8 cases), and once from this fluid he obtained a pure culture. Only once did he find the coccus in the blood of the patient during life, and this was at the moment of the death-agony.

Notwithstanding incompleteness and points open to criticism, Talamon's publication is the first in which it is clear that the author has worked with cultures of the genuine micrococcus lanceolatus obtained from lungs affected with croupous pneumonia. The name, coccus lanceolatus, which he gave to the organism is perhaps the best which it has yet received. Some French writers call it the pneumo-coccus of Talamon, in recognition of his merit in being the first to cultivate it from pneumonia.

It is also clear that in 1884 Salvioli[19a] worked with the lanceolate coccus obtained by inoculating rabbits and guinea-pigs with pneumonic sputum and exudate, and with pleuritic and pericarditic exudates from cases of pneumonia.

In April, 1884, A. Fraenkel[20] reported to the Congress für Innere Medicin in Berlin the results of his cultivation on solid media of the pneumonia coccus from the lung in three cases of croupous pneumonia. Unlike Friedländer, he found cultures of this coccus in one case pathogenic for rabbits and he missed the nail-like growth in gelatine. Friedländer pronounced this coccus to be a different organism from that which he had cultivated, and in reply Fraenkel (in a note appended to his report in the Transactions of the Congress) maintains that the organism which he has cultivated is the genuine pneumonia coccus. In this report Fraenkel calls for the first time attention to the similarity between the coccus of sputum septicæmia and that of pneumonia.

In a communication of July 13, 1885, A. Fraenkel[21] describes more fully the coccus of sputum septicæmia, which he now finds in its morphological and biological characteristics to be identical with the pneumonia coccus. The occasional presence of this organism in the mouth in health helps us to comprehend the action of the accessory causes of pneumonia, such as exposure to cold. In this as well as in the previous communication Fraenkel directs attention to the loss of virulence sustained by the pneumonia coccus in the pulmonary exudate in the course of croupous pneumonia.

In a paper read before the Pathological Society in Philadelphia, in April, 1885, and published in July, 1885, Sternberg[22] identified the micrococcus which he had previously found in his saliva, and which A. Fraenkel called the coccus of sputum septicæmia, with the micrococcus which he demonstrated in the sputum and lung of croupous pneumonia. Both Sternberg and Fraenkel, therefore, independently of each other and at about the same time, identified the genuine diplococcus pneumoniæ with the micrococcus of sputum septicæmia (Sternberg's micrococcus Pasteuri), but Sternberg fell into the error, common at the time and which he corrected in July, 1886,[23] of regarding this micro-organism as identical with the so-called pneumococcus of Friedländer.

This period of confusion was brought to an end by the exhaustive and fundamental researches of A. Fraenkel, published in 1886, the first article[24] appearing in January, the second[25] in April, and the third[26] in November. These articles furnished a full and accurate description of the leading characters of the micrococcus lanceolatus, rendered probable its causative relation to acute lobar pneumonia and many of its complications, separated this organism clearly from the pneumo-bacillus of Friedländer, and recognized its identity with the micrococcus of sputum septicæmia.

Not less important were the independent investigations of Weichselbaum,[27] communicated to the Gesellschaft für Aerzte in Vienna in May, 1886, and published in the following October. Fraenkel had cultivated the micrococcus lanceolatus from only a small number of cases of croupous pneumonia, whereas Weichselbaum's material consisted of 129 cases of pulmonary inflammation, of which 94 were genuine lobar pneumonias. He came to the conclusion that the great majority of cases of lobar pneumonia are caused by the diplocóccus pneumoniæ, but that some are caused by Friedländer's pneumo-bacillus or by a streptococcus. This eclectic view, which Weichselbaum has never abandoned, is in opposition to the conclusion reached by Fraenkel that all genuine acute lobar pneumonias are caused by the micrococcus lanceolatus.

Foà and Bordoni-Uffreduzzi[28] also deserve mention among the pioneer investigators of this period. On March 19 and 26, 1886, they reported to the Royal Academy of Medicine in Turin their observation of lanceolate diplococci in the exudate of epidemic cerebro-spinal meningitis. This micro-organism, which they called meningo-coccus, they identified with Fraenkel's pneumonia coccus and the coccus of sputum septicæmia, and in the following year they[29] published a valuable study of the biological properties of this organism.

Since these fundamental researches, each year has been rich in contributions to the literature of our subject. These have established firmly the belief in the causation of croupous pneumonia by the micrococcus lanceolatus, have extended our knowledge of the morphological and biological characters and especially of the extraordinary variability of this remarkable micro-organism, have shown that it is the cause not only of manifold complications of pneumonia but also of many diseases not associated with pneumonia, and have led to interesting discoveries concerning immunity and healing of infections caused by it. Reference will be made to many of these contributions in the course of this article.

Morphology.

As the name lanceolate coccus implies, the typical form of the pneumonia coccus is oval, with one end somewhat smaller, more tapering than the other. It is often compared in shape to the flame of a candle or to a grain of barley. It is not, however, very uncommon to find, especially in cultures, regularly oval and even spherical forms. The average length of the lanceolate cocci is about 1–1.5 μ, and is one-third to one-half greater than the width, but forms occur which are two, three, even four or five times longer than broad. These long forms cannot properly be called cocci; they are actual rods or bacilli. I have met them especially in guinea-pigs and mice, and in the subcutaneous exudate in some cases in rabbits. They may also occur in cultures. The propriety of calling this organism a coccus is open to question. Its typical form is transitional between a coccus and a bacillus, and the form may be that of an unmistakable bacillus, which is never seen in the genuine micrococci, although the latter may be at times oval. It is called a bacillus by Flügge[30] and Biondi,[31] and in a recent article by Beck,[32] from Koch's Institute for Infectious Diseases, it is called the diplo-bacillus of Fraenkel. I am inclined to the opinion that this organism is more properly designated a bacillus than a coccus, but usage is so overwhelmingly in favor of calling it a coccus that I have preferred to follow the customary nomenclature in this article.

The arrangement in pairs is so characteristic that this has given origin to the name diplococcus pneumoniæ or diplococcus lanceolatus. The pointed ends are usually those at the ends of the pair, but the adjacent ends may be pointed. Less common is the biscuit-shape which belongs to the more typical diplococci, such as the gonococcus.

Scarcely less frequent than the arrangement in pairs is that in short chains of four or six cocci. Here the subdivision into pairs is usually apparent.

Pneumococci may grow also in long and curved chains of cocci. Here, also, the subdivision into pairs and the lanceolate shape may be preserved, or the chains may be indistinguishable from the regular streptococci. This appearance is observed especially in the later generations in liquid cultures. While it is true that the greater the tendency to grow in long chains, the less virulent as a rule are the cultures, nevertheless exceptionally the pneumococcus may grow regularly in long chains both in cultures and in the animal body and still equal in virulence the ordinary diplococci, as has been observed by Foà.[33]

Starting with cultures of typical diplococci, I have sometimes obtained in later generations non-virulent streptococci which I cannot distinguish by culture methods or in any other way from some cultures of the streptococcus pyogenes. If, as there is no reason to doubt, the pneumococcus may occur under natural conditions in similar chains and with the same properties, I do not know how under these circumstances it can at present be clearly separated from some other varieties of streptococci. There are streptococcus cultures which die within a week, and others which survive many weeks or months. There is reason to believe that organisms in lobar and other forms of pneumonia have sometimes been described as streptococci without suspicion of their relation to the pneumococcus, while in reality they were varieties of this latter organism.

Streptococci and the various affections caused by them are at present among the most interesting and important objects of bacteriological study. The apparent relationship existing between the pneumococcus and certain kinds of streptococci is a matter of much interest, and it may be expected that future investigations will clear up much of the obscurity at present belonging to this subject.

Even more helpful for diagnosis than the lanceolate shape and the paired arrangement is the presence of a capsule around the cocci, the combination of these three traits having suggested the name diplococcus lanceolatus capsulatus, a designation which is generally appropriate for virulent pneumococci. Capsules are demonstrable around the cocci growing in the tissues and fluids of the animal body. The usual statement is that in most cultures the capsules are not demonstrable. They are, however, present often in blood-serum, milk and agar cultures, and sometimes in bouillon. Certain varieties present capsules in cultures more regularly and more readily demonstrable than do other varieties of the coccus lanceolatus.

The demonstration of the capsule is in some cases easy, and can be made by ordinary methods of staining; in other cases it is difficult and requires special methods. In difficult cases the following method has given me good results with cover-glass specimens:

These specimens, prepared without water, are treated first with glacial acetic acid, which is at once allowed to drain off and is replaced (without washing in water) with aniline-oil gentian-violet solution. The staining solution is repeatedly added to the surface of the cover-glass until all of the acid is displaced. If now the specimen is washed with a saturated aqueous solution of common salt and is examined in this solution, it will be seen that both coccus and capsule are uniformly and deeply stained and cannot be differentiated. If water be used instead of saturated salt-solution, the capsules are decolorized, sometimes only in part when they can be clearly recognized, but often completely and they may entirely disappear. By using weaker solutions of salt it is possible in all cases to differentiate the capsule, if it is present. The strength of the solution best adapted to different cases varies. Often the ordinary physiological solution suffices. A generally useful strength is two per cent. The specimens are to be examined in the salt solution. When mounted in balsam the cap-

sules do not always remain distinct. The capsules may appear stained throughout, or only their outer margin may be stained.

This method of staining I worked out on the supposition that the capsules are composed essentially of mucin which is precipitated by acetic acid and, when thus precipitated, is insoluble in concentrated salt solution and swells up in water.

The chief disadvantages of this method are the difficulty of avoiding precipitates of the dye, and the alterations in the cells and other elements, but in difficult cases it will serve a useful turn, although less violent methods when applicable are to be preferred.

The capsules vary in their structure, some being much more delicate and narrower than others. In old exudates the capsules are often very distinct and resistant to the action of water, in which they may appear even quite highly refractive.

The micrococcus lanceolatus stains readily on cover-slip preparations with the ordinary aniline dyes. It is less easily stained in sections. In these it can be stained by Gram's method, but Weigert's fibrin stain gives better results. The number of cocci brought to view by this last method in sections of human lungs affected with lobar pneumonia is often very great, and the presence of the majority of the cocci inside of leucocytes is clearly demonstrated.

Faulhaber,[34] who worked chiefly on the kidneys, gives the preference to Löffler's alkaline aniline water dyes, Löffler's alkaline methylene blue solution, and Kühne's carbolic methylene blue solution, in the order named.

Degenerative and involution forms of the micrococcus lanceolatus are common both in cultures and in the animal body, especially in old inflammatory exudates. Forms both larger and smaller than normal, pear-shaped, swollen, varicose forms and feebly or irregularly staining or unstained forms, are met with in old cultures and exudates. Arkharow[35] finds that in the blood-serum of rabbits rendered immune by protective vaccination, pneumococci may present degenerative forms which he describes as short, thin rods, staining imperfectly, and often staining more deeply at the slightly swollen ends. A formless detritus may result from the disintegration of the cocci.

Among the most interesting of the degenerative forms are empty capsules and capsules containing faintly staining or unstained cocci, and capsules containing small, often irregular, deeply staining particles which are evidently remnants of cocci. Ziehl[15] was the first to note the occurrence of empty capsules. Many of these degenerated capsular forms are not readily made out except by the acetic acid method just described. I[36] described these forms over two years ago as they appear by this method in empyæma. They are to be found abundantly, together with other forms of degeneration, in the exudate of croupous pneumonia, and often in rabbits in inflammatory exudates, especially those of old standing near the seat of subcutaneous inoculation. Sometimes the degenerated cocci are contained chiefly within leucocytes, but they may be abundant outside of the cells. In the later stages of croupous pneumonia it is often astounding what immense numbers of empty capsules or capsules containing dead or degenerating cocci are present, so that the exudate may consist in no inconsiderable part of these degenerated forms.

The sticky, viscid consistence often noticed in inflammatory exudates caused by the lanceolate coccus is probably often due to the abundance of capsules.

The micrococcus lanceolatus is not motile. It never forms spores.

CULTURES.

The micrococcus lanceolatus grows best at temperatures approaching that of the human body. Below 24° C. (75° F.) the growth may fail, but there may be development at as low a temperature as 18° C. (64.4° F.), especially when the organism has been cultivated for several generations outside of the body. Nutrient gelatine is not a medium adapted for obtaining first cultures of the pneumococcus, as this organism is not sure to grow at temperatures below the melting-point of gelatine.

The pneumococcus is capable of growing on all of our ordinary culture media, but there is no other known organism which will grow on so many media and at the same time is so particular as to the exact composition of the medium. Slight differences in the reaction, in the quality of the peptone and in that of the meat often determine whether or not this organism will grow. So difficult is it to control precisely these conditions that one cannot be sure that nutrient agar which may have been specially prepared is suitable for the development of the pneumococcus until he has tested it. Hence, the absence of any growth of the pneumococcus on agar not thus tested cannot be considered proof that the inoculated material did not contain this organism.

The reaction of the medium should be feebly alkaline. Agar media are best adapted for obtaining pure cultures. Plain nutrient agar, sugar agar and glycerine agar are those generally employed. My preference is for the Guarnieri[37] gelatine-agar mixture so modified as to contain more agar than in the original formula and being of a slightly alkaline instead of a neutral reaction.* On this medium the growth is particularly luxuriant.

In agar the deep colonies appear to the naked eye as minute grayish points, the surface colonies as round or slightly irregular, grayish, transparent dots, rarely exceeding 1 to 2 mm. in diameter. Under the microscope the colonies appear finely granular, and according to their thickness have a grayish or more or less of a yellowish hue. In stab cultures the growth is generally more distinct in the line of puncture than on the surface. That this organism may grow in a manner indistinguishable from the streptococcus pyogenes has already been mentioned. In such cases the colonies present the coils and peripheral chains seen in streptococcus colonies.

The pneumococcus does not liquefy gelatine. It develops well in alkaline bouillon, producing usually at first a diffuse cloudiness with small amount of sediment, followed by clearing of the bouillon, but, especially with non-virulent forms,

* My modification of Guarnieri's formula is as follows: 950 grm. meat infusion, 5 grm. NaCl, 10 grm. Merck's peptone, 6 to 8 grm. agar, 30 to 40 grm. gelatine. The gelatine and the agar are boiled separately in 50 cc. water before mixing. The reaction should be distinctly, but feebly, alkaline.

This medium partly melts at 35° C., but colonies in Petri's dishes remain separate and the medium solidifies at room-temperatures. It is not adapted for roll cultures.

there may be abundant sediment with or without clouding of the bouillon. The sediment may be pulverulent or flocculent or a uniform mass. There is produced in alkaline media a small quantity of acid.

Milk is usually soured and coagulated by the growth of the pneumococcus. Some varieties, especially non-virulent ones, do not coagulate milk. There is generally either no visible growth or a faint grayish growth on potato. Varieties, both virulent and non-virulent, occur which do not grow on solidified calf's blood-serum, whereas other varieties may grow well on this substance.

The lanceolate coccus is a facultative anaerobe, growing without as well as with the presence of free oxygen.

The variability in the properties of this coccus is manifested not less in its behavior in culture media than in other respects, varieties occurring which grow in acid media, which grow well on potato, which do not coagulate milk, which present a more opaque whitish growth than usual, etc. Important modifications in the cultural characters, particularly as to the luxuriance of the growth and the capacity of development at low temperatures, can often be brought about by artificial cultivation. Abundant growth at low temperatures is generally associated with loss of virulence and is often observed in late generations of artificial cultures of primarily virulent pneumococci. Kruse and Pansini,[38] in a recent valuable article, have fully considered the various peculiarities and modifications in the growth of the micrococcus lanceolatus.

Viability and Loss of Virulence.

One of the most striking properties of the lanceolate coccus both in the animal body and in cultures is its short viability, a property, however, which, like most of the others, is not without exceptions. The maximum development in cultures at body temperature is attained in twenty-four hours or less. After this there is usually a progressive and rapid death of the bacteria, so that they must be planted on new media in larger and larger quantities in order to obtain fresh cultures, and at the end of four to seven days surface agar cultures and bouillon cultures are usually dead. Various circumstances influence the duration of life of the cultures; absence of oxygen, exclusion of light, the proper alkaline reaction, low temperatures, and saprophytic growth for many generations prolonging their vitality. Surface agar and bouillon cultures capable of living two weeks or more are generally not virulent, but there are varieties which retain their virulence even under these circumstances.

In order to be sure of keeping the cultures alive they should be planted over every day or two. But even this precaution will not as a rule preserve the virulence of the organism. After the third or fourth generation it is not uncommon to find diminution of virulence as indicated by the later death of the inoculated animal, and frequently after about ten generations, and sometimes sooner, nearly all virulence has disappeared, although there are varieties which preserve some virulence for at least one hundred generations. In order to keep up the virulence of the cultures the plan is usually adopted of transmitting them frequently through rabbits. In my experience even this will not always succeed.

Kruse and Pansini[38] found living and virulent pneumococci in a serous pleuritic exudate which had been preserved in a sealed glass tube for over a year. Foà[39] recommends the following method for preserving the virulence of pneumococci for a long time and for obtaining material of uniform virulence. The blood of a rabbit which has died of pneumococcus septicæmia of the œdematous variety is collected immediately after death in a sterilized tube, and is put for 24 hours in a thermostat at 33°–35° C. The tube is then sealed and kept excluded from the light. In this way the virulence can be preserved for 45 days. Arkharow[35] has also found that blood withdrawn from the heart of a rabbit dead of pneumococcus infection, preserves its virulence for three to four weeks if it is kept at ordinary temperatures in sealed tubes away from the light.

Monti[40] made the interesting observation, which merits further investigation, that the impaired virulence of the diplococcus lanceolatus can be restored by injecting with the cultures into rabbits the products of the proteus vulgaris or other common putrefactive bacteria. Foà[39] found also, that the special characters of the organism were modified by the presence of some other bacteria. His meningococcus, that is the diplococcus of the fibrinogenic variety, was transformed into his pneumococcus, that is the diplococcus of the œdematogenic variety, by inoculating rabbits with a mixture of the meningococcus and the proteus vulgaris.

The short viability and rapid loss of virulence give to the micrococcus lanceolatus a quite exceptional position among pathogenic bacteria, and they constitute an annoying obstacle to systematic work with this organism, especially to experiments requiring varieties possessing maximum virulence.

The limited duration of life of the micrococcus lanceolatus is a matter of great practical interest. It is generally capable of longer life in the virulent state in susceptible animals than in artificial cultures, but it is apt to die even in the living body sooner than most other pathogenic bacteria. Mention has already been made of the large number of dead pneumococci often found in empyæmas, in the exudate of croupous pneumonia, and in local subcutaneous exudates in rabbits. This short vitality is doubtless one reason why empyæmas and other local inflammations caused by the lanceolate coccus usually afford a more favorable prognosis than those caused by streptococci, and why a single aspiration of a pneumococcus empyæma may be followed by permanent cure. But here as well as with other properties of this peculiar micro-organism, it is necessary to keep in mind the frequent exceptions to the rule, instances occurring in which virulent pneumococci are found in empyæmas and other inflammatory exudates at least six months old.

It was stated by Fraenkel[34] and Weichselbaum,[37] and the statement has been confirmed by Netter,[41] Monti,[42] Banti,[43] Patella[44] and others, that the pneumonia coccus suffers a progressive loss of virulence in the pulmonary exudate in the course of croupous pneumonia. Patella and others determined this by withdrawing with a hypodermic syringe some of the juice of the affected lung at different stages of the disease and inoculating animals. It is asserted by Netter that the expectoration on the day of the crisis often loses the virulence

which it has previously manifested and remains inactive for the following two to three weeks, although it contains living diplococci which subsequently regain their pathogenic power.

It can scarcely be doubted that attenuation of virulence does occur in the human body, inasmuch as pneumococci obtained from inflammatory exudates may be devoid of any pathogenic effect in animals, but I do not think that we are at present justified in accepting such definite laws regulating this loss of virulence as those laid down by Patella and by Netter. I have obtained from late stages of pneumonia which has gone on to recovery, and at the time of crisis, pneumococci which are as virulent and sometimes more virulent than those procured from earlier stages in the same case. In experiments of this character it is important to take into consideration the number and character of living pneumococci inoculated. We know that the pulmonary exudate contains many dead cocci, and we also know that the cocci present may vary among themselves in degree of virulence. Moreover, when we inoculate animals directly with material containing pneumococci from the animal body we may introduce with the organisms toxic, immunizing and healing substances which influence the course of the infection. It will be shown later in this article that such material, although proven to contain very virulent pneumococci, may not produce any infection. These considerations are calculated to cast doubt upon many of the experiments intended to demonstrate loss of virulence in such material as pneumonic sputum and exudate.

There is wide divergence of statement regarding the influence of desiccation on the diplococcus lanceolatus,* a divergence to be explained, according to Kruse and Pansini,[38] in large part by the characters of the particular variety used by the experimenter. Pneumonia cocci in blood and sputum are in general tolerably resistant to drying, living and retaining their virulence sometimes for four months, although they may die much sooner. Pneumococci in thin fluids like bouillon and water are less resistant to desiccation than those in animal juices. It has not been determined whether pneumococci in sputum or blood which has been dried and reduced to a dust-like powder capable of being carried by ordinary air currents can still live and be virulent. The preservation of virulent pneumococci in dried sputum for as long a time as is shown in some of the experiments, indicates the propriety of destroying or disinfecting pneumonic sputa.

A. Fraenkel[21] found that the pneumonia coccus would not grow at temperatures exceeding about 42.5° C. (108.5° F.), and that cultures at 41°–42° C. (105.8° F.–107.6° F.) rapidly lose their virulence.

According to Sternberg,[50] the pneumonia coccus is killed by exposure for ten minutes to a temperature of 52° C. (125.6° F.). It is not killed by freezing. The action of sunlight is injurious to this as well as to other bacteria.

PATHOGENIC EFFECTS IN ANIMALS.

The pathogenic properties of the micrococcus lanceolatus are of course those which most directly concern us. As regards these properties the variability of this micro-organism

*The following are the statements of different experimenters regarding the resistance of the pneumococcus to drying:

Biondi[31] (1887) impregnated sterilized silk threads in young bouillon cultures and dried them at temperatures from 18° to 35° C. The bacteria were dead in 24 hours, as tested on gelatine. Only in one instance was there trace of growth at this period. The dried silk threads were innocuous when placed, even in large amount, under the skin of rabbits at the end of 24 hours.

Foà and Bordoni-Uffreduzzi[29] (1887) found the diplococci both in cultures and in blood dried between watch-glasses at ordinary temperature away from the daylight living and virulent up to the 45th day.

Guarnieri[37] (1888) found both diffuse and direct sunlight, especially the latter, injurious to the pneumococcus cultures. Blood and sputum are more resistant to drying than are cultures. Loss of virulence is less by rapid than by slow desiccation. A rabbit inoculated with a feather dipped in blood rich in diplococci and kept for 4 months in the exsiccator at 37° C. died after 12 days with characteristic septicæmia.

Netter[45] (1888) used silk threads impregnated with blood, fragments of spleen and pneumonic sputum, and found the organisms after 32 days' desiccation still virulent.

Patella[44] (1888–89) finds, in opposition to Guarnieri, that rapid drying at 38° C. of blood containing diplococci quickly kills the bacteria, while slow drying at low temperatures preserves the virulence a long time.

Nikiforoff[46] (1890) studied a lanceolate micrococcus isolated by Gaffky from influenza pneumonia and which he considered to be distinguished from the pneumococcus, only by longer preservation of virulence and life and by failure to coagulate milk. These points, however, do not suffice to make such a distinction, as they may all belong to undoubted pneumococci. Nikiforoff's diplococcus, which was undoubtedly a variety of the diplococcus pneumoniæ, preserved its vitality and virulence for five weeks when dried on silk threads and kept in the exsiccator. How much longer the dried organism survived is not stated. Its original virulence was feeble.

Nissen[47] (1891) used silk threads impregnated with 24-hour bouillon cultures and dried in the exsiccator containing sulphuric acid. The bacteria were dead in 2 days and sometimes in 1 day. Blood containing diplococci and dried in thin layers was without infectious property after five days.

Bordoni-Uffreduzzi[48] (1891) dried small lumps of pneumonic sputum, proven to contain highly virulent pneumococci, on linen cloths at room temperature both by exposure to the air of the room with diffuse daylight and by exposure to the direct rays of the sun. The sputum after 55 days' drying exposed to diffuse light was infectious, but not after 60 days. The sputum dried by exposure to the direct rays of the sun was infectious after 12 hours; how much longer was not determined.

Sirena and Alessi[49] (1892) used silk threads impregnated with bouillon cultures or suspensions in water, and tested various methods of drying and exposure over different drying substances. They found the diplococci dead after exposure in test-tubes to direct sunlight in 3 days, after simply hanging the threads in sunlight in 17 days, after drying over calcium chloride in 31 days, over sulphuric acid in 114 days, in thermostat at 37° C. in 131 days, after keeping in dry place in the dark in 146 days, in a moist place in 192 days.

Kruse and Pansini[38] (1892) dried blood from rabbits dead of pneumococcus septicæmia in thin layer on glass plates both at ordinary temperature and in the thermostat and then kept it at 18° C. Tested by means of agar plates, one variety of pneumococcus was dead after 2 days, two varieties after 10 days, four varieties between 18 days and 3 months, and two varieties after 2 to 5 months, without reference to the method of drying. (The term variety is used here simply to indicate that the cultures were from different sources originally.) The two most resistant varieties grew luxuriantly in gelatine and were of slight virulence.

is most strikingly manifested. It is an organism of the most manifold and varied pathogenic possibilities, and one must have had a very large experience with it before he will have exhausted these possibilities. It is the cause in human beings of a large number of affections hitherto regarded as without any etiological relationship with each other. Before considering these it is desirable to learn the experimental results obtained by inoculation of animals.

We meet under natural conditions and we can readily obtain by artificial cultivation pneumococci totally devoid of any virulence, and at the other extreme we find pneumococci capable of killing rabbits by septicæmia in less than twenty-four hours. Between these extremes occur pneumococci of all possible degrees of virulence and capable of causing manifold pathological lesions.

The effects resulting from inoculation of the micrococcus lanceolatus vary with the animal, with the number of bacteria, with the degree and kind of virulence of the bacteria, and with the site of inoculation. The presence in the material inoculated of other bacteria also, as well as of their chemical products and of other chemical substances, especially such as are derived from the pneumococci themselves, may likewise influence the course and the character of the infection.

Rabbits and mice are the animals usually selected for inoculation. Mice are more certain to die than rabbits, and should therefore be used when it is desired to determine by inoculation the presence or absence of pneumococci in suspected material. I have, however, met a few cases in which mice survived and rabbits were killed by inoculation with the same exudate from croupous pneumonia, and this result could not be explained by the use of relatively larger quantity of material for the rabbit. (See Appendix, Case C.) It is well, therefore, to inoculate both a rabbit and a mouse with suspected material. Rabbits are much more suitable than mice for the study of the pathological lesions produced by the micrococcus lanceolatus. Young animals are more susceptible than old ones and, especially as regards the less virulent varieties of pneumococci, there are differences in susceptibility even between rabbits of the same age and size. The degree of resistance of the individual animal is therefore a factor of some importance.

Guinea-pigs and dogs are much less susceptible than mice and rabbits to pneumococcus infection, requiring larger doses and more virulent cultures to kill them. Kruse and Pansini[28] find that dogs are more readily killed by subcutaneous inoculation of pneumococcus cultures, than by intravenous, intratracheal or intrathoracic inoculation of even larger quantities, whereas, as has been long known, in guinea-pigs intravenous and intraperitoneal inoculations are more effective than subcutaneous ones. These animals are less prone than rabbits to develop abscesses from subcutaneous inoculations of this organism.

Rats and cats are relatively resistant, but can be infected by large doses of virulent cultures. The same is true of sheep.

Chickens and pigeons are insusceptible to even very large doses.

It is easy to demonstrate that the pathogenic effects may vary greatly according to the number of pneumococci inoculated. The three principal types of pneumococcus infection according to degree of virulence, viz., acute septicæmia, spreading inflammatory exudations and circumscribed abscess, may be produced sometimes by the same culture inoculated into rabbits in varying quantities. Here also the differences are more readily brought out by the less virulent cultures, those of extreme virulence causing septicæmia regularly, even in minute doses. When the virulence is much weakened small quantities may produce no appreciable effect, and larger quantities may kill. It is customary to use rather large doses, often as much as 1 cc. and more of fresh bouillon cultures, for ordinary inoculation with the pneumococcus.

In making comparative tests of the virulence of different cultures it is of course necessary that the conditions of the experiments should be as nearly identical as possible as regards the age of cultures, the quantity inoculated, the site of inoculation, the size of the animal, etc. As a rule, subcutaneous injections of bouillon cultures or uniform suspensions of agar cultures which are eighteen to twenty-four hours old in the thermostat, are to be preferred. A principal point in determining the degree of virulence is the duration of life of the inoculated animal. When several cultures as tested with the ordinary large doses appear to be of equal virulence, that possessed of the greatest virulence is determined by fixing the minimal dose which will kill.

We must recognize, I believe, variations not only in the degree but also in the kind of virulence. We meet with varieties of the pneumococcus which produce regularly definite pathological lesions in rabbits, and other varieties which cause uniformly different lesions, although one may kill as quickly as the other, and the conditions of the experiment as regards the animal, the age of the culture, the quantity inoculated and the site of inoculation may be identical. These differences in quality of virulence may be transmitted to successive generations of the organism, although they are frequently inconstant. While recognizing in principle variations in quality of virulence, it is by no means easy in all cases to determine to what extent different pathogenic effects depend upon differences in quantity or in quality of virulence.

Injections of virulent pneumococci into the circulation or into the peritoneal cavity of rabbits generally kill sooner than subcutaneous inoculation, and may cause septicæmia when the latter causes chiefly spreading inflammations. On the other hand, subcutaneous injections of weakened cultures may be followed by abscess formation when intravenous inoculations are without effect. Variations in the type of septicæmia may sometimes be brought out by varying the seat of inoculation. Thus, as Foà[29] has shown, the same variety of micrococcus lanceolatus which produces regularly the form of septicæmia characterized by marked subcutaneous œdema and only slight or moderate enlargement of the spleen without increased consistency of this organ, may, when injected directly into the circulation, cause septicæmia with large, hard, fibrinous spleen.

The results obtained by inoculations intended to bring out certain special localizations of pneumococcus infection, such as intra-cranial, intra-tracheal, intra-thoracic, intra-articular inoculations, will be described later.

There are sometimes striking differences in the results obtained by inoculating with material taken directly from the animal body, and with cultures of pneumococci isolated from the same material. Thus, inoculation with pneumonic sputum, pneumonic exudate, other pneumococcus exudates, the blood of rabbits dead of pneumococcus infection, may yield results different from those observed after inoculation of pure cultures from the same sources. There are various circumstances, not all of which are well understood, which appear to influence these results.

Material from the animal body, particularly old inflammatory exudates, are likely to contain degenerating and dead pneumococci, whereas fresh cultures eighteen to twenty-four hours old contain mostly living organisms. It has been demonstrated by making cultures from different colonies growing in plate cultures from pneumonic sputum or pneumonic exudate, that pneumococci of different degrees and of different kinds of virulence are often mixed together in such material. That in the course of croupous pneumonia and other pneumococcus infections the primary virulence may be weakened has already been mentioned. It has furthermore been shown that during pneumococcus infections there are developed in the body toxic, immunizing and healing substances, and these may be inoculated with the micro-organisms and modify in various ways the course of infection or arrest it altogether, or cause death by intoxication without multiplication of the organisms.

It is evident from the foregoing considerations that there are many factors which influence the result of inoculation with material containing the micrococcus lanceolatus. It is evident that we must not lose sight of these various factors in drawing conclusions as to the degree and kind of virulence possessed by micrococci lanceolati from different sources.

The principal symptoms which may be observed in rabbits inoculated with virulent micrococci lanceolati are fever, diarrhœa and occasionally albuminuria. The temperature is elevated often in a few hours after subcutaneous inoculation and before the appearance of cocci in the circulation. Indeed, even in acute septicæmias where many cocci are found in the blood after death, the organisms can be demonstrated in the circulation often only a few hours before death. They may, however, be present in the blood as long as forty-eight hours before death. Diarrhœa may occur, but it is far from constant. An excess of albumen in the urine beyond physiological limits is a less common symptom, but I have repeatedly noted it. The general condition of the animal is usually surprisingly good until within a few hours of death. At the last the animal becomes weak and stupid. The head droops. Convulsive seizures are not uncommon shortly before death. The animal may cry out. Pulmonary œdema sometimes accompanies the death-agony and may be manifested by frothy serum around the nostrils. In subacute and chronic cases there is loss of weight and there may be profound anæmia. With inflammatory exudates leucocytosis is present.

The lesions found post mortem in rabbits are many and vary with the type of the infection.

Septicæmia is regarded as the leading type of pneumococcus infection. With this the rabbit may die in 16 to 24 hours, but often lives from 48 hours to 4 days. It is possible, therefore, to distinguish peracute, acute and subacute pneumococcus septicæmias. If death takes place after four or five days there will generally be found spreading inflammatory exudations or abscess formation, with few or no bacteria in the blood.

Before considering the different types of septicæmia caused by the micrococcus lanceolatus, the lesions which may be found in different parts of the body will be described. This description applies chiefly to rabbits.

If the inoculation be subcutaneous, local reaction at this point is rarely entirely absent. It may be predominantly serous or fibrinous, or hemorrhagic or necrotic or purulent. Frequently there are combinations such as fibrino-purulent, fibrino-serous, sero-hemorrhagic. The longer the duration of the disease the greater the tendency to fibrinous and to purulent exudations. The extent of reaction varies. It may be limited to the immediate seat of inoculation or, if serous or fibrinous, it may extend over a large part of the body. Frequently at the immediate seat of inoculation there is an opaque exudate of fibrin and leucocytes or of pus, and around this a spreading œdema. Ecchymoses and larger hemorrhages are common. The exudation may extend in depth from the epidermis to the muscles, or to the serous membrane if the inoculation be in the abdominal or thoracic subcutaneous tissue. There may be coagulation necrosis with much nuclear fragmentation of the tissue cells. The lymphatics may be plugged with inflammatory products.

The subcutaneous lymphatic glands, particularly those in communication through lymphatic channels with the seat of inoculation, are often swollen and hyperæmic or even hemorrhagic. They may contain small whitish spots which under the microscope show necrosis with nuclear fragmentation, combined usually with an accumulation of leucocytes and sometimes of fibrin. The lymphatic glands may also be swollen and pale, or red and not swollen, or they may be unaltered.

There are sometimes seen in the cutaneous and subcutaneous tissues of the trunk, particularly on the dorsal aspect, scattered, irregular, opaque whitish or reddish-white, circumscribed areas two to ten mm. in diameter, which correspond to spots where the cutaneous striated muscle has undergone necrosis with fatty and hyaline (pseudo-waxy) degeneration and often marked vacuolization and disintegration of the fibres. These areas usually contain extravasated blood, especially in the periphery. Similar alterations may be found in the voluntary muscles of the extremities and elsewhere, and occur after intravenous as well as after subcutaneous inoculations.

The spleen may be normal in size and appearance. Usually it is swollen. This enlargement may be moderate or excessive. As regards consistence, two types are observed, the hard and the soft spleens. The typical hard spleens may be dark red, almost black, or they may be light red or mottled. They are dry on section, suggesting sometimes in appearance hemorrhagic infarction. They contain a great quantity of fibrin, which can be well demonstrated by Weigert's fibrin stain, and a large amount of blood. They show more or less fragmentation of the nuclei. The soft spleens do not contain an excess of fibrin. They are rich in blood and often contain blood pigment. There may be no change in the consistence of the spleen.

The liver often contains, in variable number, small, opaque, whitish or yellowish-white dots of necrosis. This is in my experience a frequent lesion of septicæmia caused by the micrococcus lanceolatus, and it is curious that its frequency and generally its existence should have been overlooked by previous observers. The necroses are usually visible as whitish dots and streaks about 1 to 2 mm. in diameter, most readily seen on the surface, but present also in the depth of the liver. They may be discovered microscopically, when not apparent to the naked eye. They cannot readily be mistaken for parasitic nodules, often seen in the rabbit's liver. In the necrotic foci the nuclei of the liver cells are in large part absent or fragmented, the cell body becomes more opaque and refractive than normal and may contain fatty globules and may have a reticulated structure suggesting fibrin, but without the reaction of fibrin. Polynuclear leucocytes wander in from the edges, the liver cells gradually diminish in size or break up and disappear, leaving a peculiar network of intervening glistening lines. Similar foci of hepatic necrosis occur in typhoid fever, hog cholera and many other bacterial infections. I have found them in the liver of human beings dead of croupous pneumonia and in many other infectious diseases in human beings. It has been shown by Dr. Flexner and myself[51] that the presence of bacteria in the liver is not essential to their production, but that they may be caused by the toxic products of bacteria. Cloudy swelling and fatty degeneration of the hepatic cells are common.

The kidneys show often no especial lesion. The renal epithelium may be more or less fatty, and fatty globules may be seen in the glomeruli. The most interesting change observed in the kidney is the presence of hyaline material in the glomerular and intertubular capillaries. This lesion is common in certain types of pneumococcus septicæmia and rarely occurs in others. The hyaline material stains deeply with Weigert's fibrin stain and I regard it as a form of fibrin. It seems to me to be within the capillaries and often plugs them completely. It has been usually described as situated in the perivascular spaces. This capillary thrombosis may be so extensive as to prevent any artificial injection of fluid into the blood-vessels of the kidney. In such cases there is almost complete anuria. Similar capillary thrombosis may be met with in other parts of the body.

The heart muscle is in nearly all cases the seat of fatty degeneration and often extremely fatty. In septicæmias terminating within 18 or 20 hours there may be no fatty degeneration of the myocardium.

The blood is usually found coagulated in the heart and vessels. The right ventricle is often greatly distended with coagula, which may be partly decolorized. The blood may be fluid and the right ventricle small. Leucocytosis is common, and the increase is chiefly of the leucocytes with amphophilic granulation.

Redness of the tracheal mucous membrane and pulmonary œdema are sometimes observed. The lungs may be normal or may present ecchymoses or, especially in cases of long duration, may contain smaller or larger areas of hepatization.

Swelling and hyperæmia of the thyroid and thymus glands are occasionally seen.

Œdema of the mediastinal and subperitoneal tissues may occur. There may be increase of serum in the peritoneal and other serous cavities.

Inflammation of one or more serous membranes is common in infections with certain varieties of the micrococcus lanceolatus and is rarely or never observed with others. When it occurs the affection is usually of several days' duration, but multiple serositis may be observed in septicæmias not more than 48 hours in duration. Peritonitis is the most common after subcutaneous or intravenous inoculations, but there may be pleuritis, pericarditis and peritonitis together.

The intestinal contents may be unchanged or they may be softer than normal. Hemorrhages may occur in the intestinal coats, and I have seen necrotic and diphtheritic patches of inflammation in the cæcum and colon. The same may also, although very rarely, occur in the mucous membrane of the gall bladder.

Semi-purulent exudations in the joints have been noted in some cases.

Subserous, particularly subperitoneal, ecchymoses are common. An infrequent type is the markedly hemorrhagic septicæmia with hemorrhages, sometimes extensive, in the subcutaneous tissue, lymph-glands and many or most of the organs of the body.

In septicæmia pneumococcica capsulated diplococci are abundant in the serous and inflammatory exudates, if these are present, and are usually abundant in the blood and organs. There may, however, be few cocci in the blood, even in rapidly fatal cases. In cases lasting more than 48 hours the number of cocci in the subcutaneous exudate may be smaller than in the blood and in exudates in the serous cavities. In such cases the subcutaneous exudate usually contains many degenerated cocci, such as have been already described. The diplococci are usually free, but may be within leucocytes, especially in inflammatory exudates. I have seen in a case of multiple serositis most of the diplococci in the pleural exudate within leucocytes, and in the peritoneal exudate extracellular.

It is apparent from the foregoing description that there is much variety in the lesions of pneumococcus septicæmia, cases occurring in which there are scarcely any lesions, and other cases in which there are many localizations of the morbid process. The alterations which may occur in one and the same organ, as the spleen, differ widely in different cases.

The attempt has been made to establish distinct varieties of the micrococcus lanceolatus on the basis of these diverse pathological effects. The usual statement, however, is that these differences are inconstant, that they depend upon variations in the degree rather than in the kind of virulence of the coccus, that one and the same variety of coccus lanceolatus may produce now one and now another type of septicæmia.

Those who attempt to distinguish distinct biological varieties of the coccus lanceolatus do not agree with each other in their classification. Banti[52] makes four varieties and considers that these are only a part of the whole number. His researches are valuable, but his classification has not been confirmed and will not be here considered. More importance in my opinion is to be attached to the distinctions made by Foà and his col-

laborators in various publications.[13] Foà distinguished originally his meningococcus from the pneumococcus, and even suggested that they were perhaps two distinct species of bacteria. He has modified in several particulars his earlier statements on this point, and only his later views need be here presented. The variety to which he and Bordoni-Uffreduzzi first gave the name of meningococcus.he now prefers to call diplococcus lanceolatus of the fibrinogenic (or parasitic) variety, and the second variety, his pneumococcus, he calls diplococcus lanceolatus of the œdematogenic (or toxic) variety. Both varieties may occur alone or mixed in the lung in croupous pneumonia, but the œdematogenic variety is the more common in this situation. He has hitherto met in the exudate of epidemic cerebro-spinal-meningitis only the fibrinogenic variety. The fibrinogenic variety is characterized by the rapid invasion and multiplication of the cocci in the blood (hence also parasitic variety), and especially by the firm, fibrinous spleen, and fibrinous thrombi (hyaline) in the kidney and elsewhere. The chief characteristic of this variety is the separation of fibrin in the blood. It does not produce local œdema. On the other hand, the œdematogenic variety is characterized by slower multiplication and this chiefly after subcutaneous inoculation in the subcutaneous tissue, where it produces often widely spreading œdema. There are relatively few cocci in the blood, the spleen is soft and contains disintegrated red blood corpuscles, there are no fibrinous thrombi (hyaline) in the kidney or elsewhere. This variety he also calls toxic. Foà now admits that in addition to the fixed types of these two varieties there occur transitional forms in which the type is not fixed and which may produce lesions belonging to both varieties. Pneumonic sputum and exudate may contain both varieties, and when inoculated into rabbits produce both œdematous and fibrinous lesions. The differences between the œdematogenic and the fibrinogenic varieties, he says, cannot be attributed merely to differences in degree of virulence, as one may kill as surely and as speedily as the other. They correspond therefore to different biological attributes, to different qualities of virulence. The œdematogenic variety, when injected directly into the circulation, often, but not invariably, produces hard, fibrinous spleens, and even after subcutaneous inoculation it may do so if the fibrin factors in the blood be increased, as by pregnancy, but it preserves its specific properties when introduced subsequently under the usual conditions into the subcutaneous tissue of rabbits. When cultivated anaerobically it can be made to assume the properties of the fibrinogenic variety. This latter variety can be transformed into the œdematogenic when inoculated in combination with certain other kinds of bacteria, particularly the proteus vulgaris.

I have met varieties of the micrococcus lanceolatus which correspond to Foà's classification, but I am not able to draw the lines of separation as sharply as he does, as in my experience types with inconstant or mixed characters are common. I have, however, obtained cultures which, when injected subcutaneously, produce uniformly extensive local subcutaneous œdema with soft or unchanged spleen, and relatively few organisms in the blood. I have inoculated in series twelve rabbits, varying the dose so that death occurred in sixteen hours up to four days, and have seen no change in the type of septicæmia, especially no hard or fibrinous spleen. This, therefore, corresponds to Foà's œdematogenic variety of fixed type. I have also obtained cultures which produced after subcutaneous inoculation uniformly hard, firm spleens. These differences could not be explained by diversities in the degree of virulence, as with each variety the results were the same after death in 24 hours or 4 days. We must recognize, therefore, varieties of the micrococcus lanceolatus with different biological attributes. I have also obtained from single colonies pure cultures which produced a mixed type of septicæmia, that is, subcutaneous œdema with hard fibrinous spleen, with or without an abundance of cocci in the blood, or combined fibrinous and serous subcutaneous exudation with varying character of spleen. I have repeatedly found that cultures or direct inoculations from a rabbit dead of one type of septicæmia produced in a second rabbit the other type of septicæmia. The occurrence of fibrinous (hyaline) thrombi in the kidney is not necessarily associated with the hard, fibrinous spleens; one may be present in the absence of the other, especially may the change in the kidney be absent when the spleen is firm and rich in fibrin.

The presence in the blood of very large numbers of diplococci is not necessarily associated with a hard, fibrinous spleen. I have found the blood swarming with typical capsulated diplococci without any change in the consistence or size of the spleen, as well as with soft and with hard spleens.

The changes in the heart, liver and lymphatic glands above described are common to all the varieties of septicæmia produced by the micrococcus lanceolatus.

The pathological effects resulting from inoculation of the micrococcus lanceolatus depend, as has already been urged, upon many factors, of which differences in degree and kind of virulence are among the most important.

A second type of pneumococcus infection in rabbits may be conveniently distinguished, although it cannot be sharply separated from the septicæmic type. This second type, which is common, is characterized by spreading, localized, usually multiple, sero-fibrinous or fibrino-purulent inflammations without many cocci in the blood. There is evidence that this exudative type depends upon weakened virulence of the cocci. Rabbits affected with this form of the disease live usually from five to fifteen days and sometimes longer. Pneumococci which at first are of sufficient virulence to produce acute septicæmia, are prone to cause this exudative type when their virulence is weakened, and on the other hand by the passage of the organism through the rabbit the septic type can sometimes be established. Very virulent pneumococci may produce this exudative type in rabbits rendered partly immune against infection.

The subcutaneous tissues for a wide distance around the point of inoculation are thickened and indurated by infiltration with a dense exudate of fibrin, leucocytes and more or less serum, associated often with extravasated blood and with coagulation necrosis of the tissues. In the outlying parts there is inflammatory œdema, sometimes hemorrhagic in character. If the inoculation has been in the subcutaneous tissue of the abdominal wall the exudation may spread over the cor-

responding side of the abdomen and thorax, over to the opposite side and down the thigh. It may involve the cutis and the intermuscular septa down to the serous membrane. In rare instances this spreading subcutaneous fibrino-purulent exudate is the sole or principal pathological lesion, and it may occur without any bacteria in the blood or internal organs at the time of death.

In the majority of cases there are associated with the subcutaneous exudation similar fibrino-purulent inflammations of the serous membranes, oftenest of the peritoneum, but not infrequently also of the pleuræ and pericardium. There may even be pneumonic areas.

The spleen is often little or not at all changed. Large, hard, fibrinous spleens belong rather to the septicæmic type, but there is no relation between the size of the spleen and the number of cocci present in it and in the blood. Indeed, the small spleens in the septicæmic type are often notably rich in cocci.

Foci of hepatic necrosis and fatty degeneration of the heart occur in this as well as in the preceding type of infection.

When the disease is of long duration the animal becomes notably emaciated and anæmic. There is commonly marked increase in the number of leucocytes.

When this second type of the disease is outspoken, there are few cocci in the blood, so few often as not to be readily demonstrable on cover-glass preparations, although demonstrable by cultures. On the other hand, the local exudates contain the characteristic cocci often in enormous number. The cocci may, however, be relatively few or even absent in the subcutaneous exudate which contains many degenerated forms. These forms may be seen also in other exudates.

In the exudative and also in the septicæmic types diplococci may be found in the bile and in the intestinal contents. They are absent from the urine, except in some cases with focal lesions of the kidney due to the presence of the cocci.

No sharp line of separation can be drawn between the first and the second types of pneumococcus infection. All grades of transition between them occur and mixed types are common. As has already been mentioned, the differences between these two types depend rather upon the degree than upon peculiarity in the quality of virulence.

In this connection it may be noted that croupous pneumonia in human beings belongs to the exudative rather than the septicæmic type of pneumococcus infection. Inasmuch as the occurrence of such spreading inflammations with little or no invasion of the blood by pneumococci is experimentally shown to depend chiefly upon the relation existing between the virulence of the coccus and the resistance of the animal, and as we cannot suppose that the pneumococci which cause croupous pneumonia are of weakened virulence, the inference is drawn that man ranks among those relatively insusceptible to this organism.

A third type of disease caused by subcutaneous inoculation of the diplococcus pneumoniæ is the formation of an abscess at the point of inoculation. This occurrence indicates either still less virulence than in the preceding types, or, with the same virulence, greater resistance on the part of the animal. Rabbits which have been rendered sufficiently immune to be protected against septicæmia after inoculation with virulent diplococci often acquire a local abscess at the point of inoculation.

The micrococcus lanceolatus under these conditions is an exquisitely pyogenic micro-organism. The abscess which forms at the point of inoculation may be small or large. Usually the animal recovers.

There may be a combination of purulent formation with the preceding types of pneumococcus infection. Thus it is not uncommon to find small purulent foci mingled with the fibrinous exudation in the subcutaneous tissue. The first effect of subcutaneous inoculation may be an indurated spreading fibrinous exudation, and in course of time this may be resolved into one or more abscesses, with recovery of the animal.

An interesting but rare form of pneumococcus disease is that in which there are multiple suppurative processes in the body. These occur especially in the joints and in the serous cavities. In the Appendix, Case F, is related an example of purulent pleurisy and pericarditis, with localized subcutaneous abscess following subcutaneous inoculation, without pneumococci in the blood and organs, although the cocci were abundant in the pus. It is noteworthy that in animals as well as in man the pneumococcus is capable of producing not only fibrinous but also genuinely purulent multiple inflammations of the serous membranes without septicæmia.

Foà and Carbone[25] have observed that occasionally a rabbit which has been inoculated with pneumonic exudate taken from the dead body dies with symptoms of marasmus after 8 to 15 days, without any micro-organisms in the blood and tissues. They infer that the diplococci were dead, leaving behind only the poison which they have produced. Other experimenters have had similar results. I have also met similar cases not only after inoculation with pneumonic exudate, but also after inoculation with the blood of rabbits dead of typical pneumococcus septicæmia. Such a case of peculiar interest is related in the Appendix, Case C, Exp. 5. In this instance a rabbit, the third in series, was inoculated subcutaneously with 0.8 cc. of the heart's blood of a rabbit which had just died of typical pneumococcus septicæmia, 48 hours after inoculation, with many characteristic diplococci in the blood which developed pure in the cultures. This third rabbit died 15½ days after the inoculation without any living bacteria at the seat of inoculation, or in the blood and tissues, but with the most exquisite focal necroses in the liver and other evidences of toxæmia. As these lesions have not hitherto been described as the result of intoxication with the poison of the diplococcus pneumoniæ, I would call special attention to the protocol of this experiment. The explanation of the result in this case seems to me to be that with the pneumococci are introduced substances possessing both toxic properties and healing or immunizing properties. The peculiar result seems attributable to the mutual reaction of these different factors. This view is supported by the observation which has been made that rabbits may die in a similar way, without micro-organisms in the blood and tissues, after simultaneous inoculation of virulent pneumococcus material and healing blood-serum (Foà and Carbone). It is not very uncommon for mice to die in two to six days after inoculation with pneumococcus material with-

out any bacteria being demonstrable in the blood and tissues after death.

The possibility of the recovery of rabbits after actual infection or intoxication has followed inoculation with pneumococcus material cannot, I think, be denied, but we possess very little information on this point. There are occasionally late deaths without apparent cause one or two months or more after such inoculation. We pay in general too little attention in our experiments to these remote effects of bacterial inoculation. I have recently killed, three months after inoculation, a rabbit which for a week seemed to be very ill after inoculation with a pneumococcus culture which had killed a mouse with acute septicæmia in 36 hours. The rabbit did not develop an abscess and had apparently entirely recovered. I found the liver enlarged, very hard and pale, somewhat suggestive of waxy degeneration which was not present. This liver was the seat of extensive diffuse cirrhosis with so-called multiplication of the bile-ducts. There were no psorosperms or other parasites present. No micro-organisms could be found. In view of the necrotic changes so commonly found in the livers of rabbits dead of pneumococcus infection, it does not seem improbable that the cirrhosis was dependent upon the inoculation from which the animal had evidently suffered three months previously. Banti[53] reports two cases of hepatic cirrhosis in guinea-pigs resulting from chronic infection following peritoneal inoculation of one of his varieties of the pneumococcus.

It has already been mentioned that the micrococcus lanceolatus may be present in inflammatory exudates, including croupous pneumonia, as well as in cultures in a condition totally devoid of virulence, incapable of producing any demonstrable lesion or effect even in mice.

Having now passed in review the varied pathological effects which follow the ordinary subcutaneous or intravenous modes of inoculation, we turn to the efforts which have been made by special mode of inoculation to produce certain definite localizations of the morbid process.

In general it may be said that whether the inoculation be under the skin, into the circulation, into the serous cavities, into the cranial cavity, into the lungs or into the articular cavities, results similar to those already described are obtained, but some points of especial interest have been brought out by these diverse methods of inoculation.

The chief interest attaches to the efforts which have been made to reproduce in animals acute lobar pneumonia.

It is not very uncommon to find in pneumococcus infections of rabbits after subcutaneous or other methods of inoculation circumscribed areas of pulmonary hepatization. Intra-tracheal and intra-pulmonary inoculations and inhalations of pneumococci have been resorted to for the purpose of producing with greater certainty pneumonia. The results obtained by different experimenters have varied considerably.

Emmerich[54] reported to the Seventh International Congress of Hygiene in London, in 1891, that Doenissen, working under his direction, had found that an hour's inhalation of sprayed bouillon cultures of pneumonia diplococci produced invariably in rabbits pneumonia and death in two to four days.

The injection of very virulent pneumonia cocci into the lungs or into the trachea of rabbits is usually followed, as might be expected, by acute septicæmia without especial localization in the lungs. It is evident that in order to produce pneumonia in this way we must either select pneumococci of weakened virulence so that they will not kill by quick septicæmia, or we must choose animals less susceptible than the rabbit and which respond to highly virulent pneumococci by spreading local inflammation rather than by acute septicæmia.

The early investigators, A. Fraenkel,[24] Weichselbaum[27] and Foà and Bordoni-Uffreduzzi[29] found that the intra-pulmonary injection of pneumococcus cultures in rabbits is often followed by pleurisy, pericarditis and lobular or even lobar pneumonia, and these observations have been repeatedly confirmed. Monti[43] produced by intra-tracheal injection of cultures three to five days old in rabbits, "typical fibrinous pneumonia" of one lobe or of an entire lung, often complicated by pericarditis and sometimes almost without any general infection. The result, he says, depends on the mode of inoculation, the degree of attenuation of the organisms and the strength and development of the animal. Young animals responded by general infection sometimes when old ones acquired typical pneumonia. Lipari[55] claims that the susceptibility of rabbits and guinea-pigs to pneumonia by intra-tracheal inoculation of attenuated pneumococcus material can be heightened by exposure to cold.

Gamaleia[56] claims to have produced in many instances typical fibrinous lobar pneumonia by the injection of extremely virulent pneumococcus cultures in large doses into the lungs of dogs and sheep.* Endo-tracheal inoculations were without effect in these animals unless preceded by the injection of irritating substances like tartar emetic.

Tchistovitch[57] inoculated cultures of the pneumococcus into the trachea of 19 dogs. Of these three died of pneumonia, four acquired benign pneumonia (of these four, three were killed and one recovered), and the remaining twelve bore the inoculation without notable reaction, except temporary elevation of temperature.

It is not to be doubted from the observations mentioned, and many more might be collected in the literature of this subject, that under certain conditions the micrococcus lanceolatus is capable of causing acute lobular and even lobar pneumonia in animals. The statements of writers are often positive as to the identity of some of these experimental pneumonias with acute lobar pneumonia as it occurs in man. On this point, however, I think there is room for scepticism. Acute lobar pneumonia as it occurs in human beings is a very definite and well characterized affection both anatomically and clinically. So far as known, the domestic animals are not

*These experiments of Gamaleia seem conclusive enough, but they are not described with sufficient detail to permit critical judgment, nor have they been satisfactorily confirmed by other investigators. Many inoculations of cultures of virulent pneumococci into the trachea and lungs of dogs have been made in my laboratory by Dr. Canfield and myself, but in no instance were we able to produce an inflammation of the lungs which we were willing to identify with acute lobar pneumonia as found in human beings. In the majority of our experiments there was no appreciable effect; in a few pleurisy and more or less extensive areas of pneumonia were produced. Our experience in this respect is analogous to that of Kruse and Pansini. The experiments cited of Monti and Lipari also await confirmation.

subject to a form of pneumonia etiologically and anatomically identical with croupous pneumonia of man. Bacteriologists are not always pathologists, and the bare statement that the pneumonia produced experimentally is in all respects identical with acute lobar pneumonia in human beings should be received with caution. But fortunately it is not necessary to insist upon the absolute identity of the experimental pneumonias caused by the pneumococcus with human acute lobar pneumonia. We possess conclusive experimental proof that the diplococcus pneumoniæ is capable of producing spreading inflammatory exudates with all of the characteristics of the exudate in croupous pneumonia as it occurs in man. The evidence that this micro-organism is the cause of acute lobar pneumonia in man rests upon many points which will be summarized later in this article and which seem to constitute incontrovertible proof.

As the micrococcus lanceolatus is the cause of many cases of cerebro-spinal meningitis (hence the name meningococcus), the attempt has been made to reproduce this lesion experimentally. A. Fraenkel[25] says that he has not been able to produce meningitis by inoculation, but the method of inoculation is not stated. Foà and Bordoni-Uffreduzzi,[28] by subdural inoculation of a meningococcus culture, produced in the rabbit "general infection with swelling of the spleen and meningitis endocranica totalis and hyperæmia of the spinal meninges." Similar results are reported by Netter,[45] Weichselbaum[58] and others. In these cases the exudation was very slight. Monti[42] produced by submeningeal inoculation in dogs of 24 hour pneumococcus cultures "typical cerebro-spinal meningitis," while the corresponding experiments in rabbits gave less typical results.

Endocarditis is a very rare result of simple subcutaneous or intravenous inoculation, but it has been observed by Kruse and Pansini[38] and by Vanni.[59] It can be produced by the well known method adopted for causing infectious endocarditis, viz., by first injuring the valves by means of a sterilized probe passed from the carotid artery into the left ventricle and then injecting the cultures. In this way first Netter[60] and then Guarnieri[37] have succeeded in producing experimentally in rabbits by injection of pneumococcus cultures, vegetative and ulcerative endocarditis.

Gabbi[61] has produced experimentally in rabbits arthritis and periarthritis by direct injection into the joints of pneumococcus cultures, and also by subcutaneous injection following injury of the joint by traumatism or irritating substances.

Zaufal[62] has produced otitis media by inoculation of pneumococci into the tympanic cavity of animals.

It is evident from the foregoing review of the pathogenic effects produced by the micrococcus lanceolatus in animals, that we possess a rich mass of experimental data to aid us in explaining the multiform manifestations of infection by this micro-organism in human beings.

The question as to how far we are justified in recognizing distinct varieties of the diplococcus pneumoniæ will be answered differently by different bacteriologists, according to one's conception of the meaning in biological classification of the term variety. Those who insist that in order to justify the designation variety there should be a considerable degree of fixity and transmissibility of distinctive characters will find it difficult to establish well-defined varieties of this organism. It seems to me, however, that we must give a somewhat looser meaning to the term variety in the classification of bacteria, and that we cannot conveniently dispense with this word in speaking of the different modifications of the micrococcus lanceolatus. These modifications are endowed, as we have seen, with very diverse pathogenic attributes.

Transmission of Infection from Mother to Fœtus.

In this connection a few words may be said concerning the transmission of the pneumococcus from the mother to the fœtus in utero and concerning the presence of the organism in the secretion of the mammary gland.

It is well known that acute lobar pneumonia developing during pregnancy is likely to bring about miscarriage. The same is to be noticed in mice and rabbits inoculated with virulent pneumococci. Neither in human beings nor in animals does abortion necessarily attend pneumococcus infection.

The transmission of pneumococci from the mother to the fœtus has been demonstrated both in human beings and in animals.

In the human cases reported as intra-uterine infection (only those in which a satisfactory bacteriological examination was made are here considered) by Netter,[63] Levy,[64] Birch-Hirschfeld[65] (first of his two cases) and Viti[66] the infants died two to five days after birth and, although the infection was probably intra-uterine, the possibility of its occurrence during or after birth cannot be absolutely excluded. Foà and Bordoni-Uffreduzzi,[29] however, report finding pneumococci in the blood and liver of two human embryos of the fourth and of the sixth month born on the second and the third day of croupous pneumonia in the mother. Diplococci were present also in the uterine veins and the placenta. Birch-Hirschfeld's[65] second case is a particularly satisfactory one. On the fourth day of croupous pneumonia the mother gave birth to a seven months' still-born fœtus with intact membranes. There were hemorrhages in the maternal and the middle parts of the placenta. The only lesion noticed in the fœtus was ecchymoses in the renal pelvis. Typical virulent pneumococci were found by culture in the liver, heart's blood and umbilical vein of the fœtus, also in the placenta.

Actual pneumonia existed only in the infants who had lived some hours after birth, so that Netter concludes that it is necessary that the child should have breathed in order to acquire localization of the pneumococcus infection in the lung. As the still-born infants presented no characteristic lesion, only a bacteriological examination could have determined the existence of the infection.

It is probable that the transmission of pneumococci from mother to fœtus is exceptional in the case of human beings. Levy did not find any organisms in a five months' fœtus born when the mother was affected with croupous pneumonia.

There must of course have been pneumococci circulating in the blood of the mother in order to produce intra-uterine infection, and in addition it is probable that some lesion of the placenta, such as hemorrhages, is, if not absolutely necessary, at least an important predisposing factor.

In pregnant rabbits with pneumococcus septicæmia infection of the fœtus in utero is far from constant, but it has been repeatedly observed.

Ortmann[67] has seen metritis and endometritis in a pregnant guinea-pig infected with the diplococcus lanceolatus.

Foà and Bordoni-Uffreduzzi[29] were the first to note the presence of pneumococci in the milk of pregnant rabbits inoculated with the virulent organism. They furthermore obtained diplococcus septicæmia in young rabbits which sucked the breast of the mother infected with the lanceolate coccus. The same authors have found pneumococci in the milk of women affected with croupous pneumonia, and this observation has been confirmed by Bozzolo.[68] We have no information as to the frequency of this occurrence.

(To be continued.)

MEDICAL SCHOOL OF THE JOHNS HOPKINS UNIVERSITY.

Miss Mary E. Garrett, of Baltimore, under date of December 22, 1892, addressed the following letter to the President and Board of Trustees of Johns Hopkins University:

In the resolutions of your Board of Trustees, adopted on October 28, 1890, it was provided that the Medical School of your University should be opened when a general fund had been accumulated for its establishment and maintenance amounting to not less than $500,000.

In the minute of your Board of Trustees, adopted on April 30, 1891, it was stated that the University would have in money and property applicable to its Medical School fund when it received the Women's Medical School Fund the sum of $178,780.42. This sum, because of subsequent paymonts, outstanding collectable amounts, and the interest accrued thereon, may now be safely assumed to be $193,023.

It is necessary, therefore, that the general fund referred to should be increased by the sum of $306,977 to insure the opening of your Medical School. I now place this amount of $306,977, payable as hereinafter provided, at the disposal of your Board of Trustees for the use of its Medical School upon the terms expressed in your resolutions of October 28, 1890, and upon the terms expressed in my letter of April 27, 1891, and accepted in your minute of April 30, 1891, namely, that this sum of $306,977 shall revert to me, or such person or persons, institution or institutions, as I, by testament or otherwise, may hereafter appoint, if the University shall discontinue a Medical School devoted to the education of both men and women, or if at any time it can be shown by proper legal proceedings that the women studying in the Medical School do not enjoy all its advantages on the same terms as men, or are not admitted on the same terms as men to all prizes, dignities or honors that are awarded by competitive examination or regarded as rewards of merit, and with certain further stipulations, as follows:

"1. That not more than $50,000 of the original endowment of $500,000 shall be expended on a building or buildings, and that in memory of the contributions of the committees of the Women's Medical School Fund this building, if there be but one, or the chief building, if there be more than one, shall be known as the Women's Fund Memorial Building.

"2. That the Medical School of the University shall be exclusively a graduate school as hereinafter explained, that is to say: That the Medical School of the Johns Hopkins University shall form an integral part of the Johns Hopkins University, and, like other departments of the University, shall be under the management and control of the Trustees of the said University; that it shall provide a four years' course, leading to the degree of doctor of medicine; that all the instruction given in the school shall presuppose the knowledge at present required for matriculation in your University, and the knowledge imparted in the preliminary medical course (*Third Group*, Chemical Biological) as at present laid down in your University Register; but there shall be admitted to the school those students only who, by examination or by other tests equally satisfactory to the faculty of the Medical School (no distinction being made in these tests or examinations between men and women), have proved that they have completed the studies included in the preliminary medical course (but this condition is not meant to restrict the Trustees from receiving as hearers, but not as candidates for the degree of doctor of medicine, those who have received the degree of doctor of medicine, or its equivalent, in some school of good repute,) and that the degree of doctor of medicine of the Johns Hopkins University shall be given to no doctors of medicine who have not proved by examination, or by other tests equally satisfactory to the faculty of the Medical School, that they have completed the studies included in the preliminary medical course, besides completing the course of instruction of the Medical School of the Johns Hopkins University.

"3. That the terms of this gift and the resolution of October 28, 1890, in which the Trustees accepted the gift of the Women's Medical School Fund, shall be printed each year in whatever annual or semi-annual calendars may be issued announcing the courses of the Medical School.

"4. That there shall be created a committee of six women to whom the women studying in the Medical School may apply for advice concerning lodging and other practical matters, and that all questions concerning the personal character of women applying for admission to the school and all non-academic questions of discipline affecting the women studying in the Medical School shall be referred to this committee, and by them be in writing reported for action to the authorities of the University; that the members of this committee shall be members for life; that the committee, when once formed, shall be self-nominating, its nominations of new members to fill such vacancies as may occur being subject always to the approval of the Board of Trustees of the University, and that the first members shall be Mrs. Henry M. Hurd and Mrs. Ira Remsen, both of whom were active members of the Baltimore committee of the Women's Medical School Fund; Mrs. William Osler, Miss M. Carey Thomas and Miss Mary M. Gwinn, the two friends who have been most closely associated with me in promoting the opening of the Medical School, both of whom are daughters of Trustees of the University, and myself.

"5. That the Medical School shall be opened in the autumn of 1893, and that notice of such intended opening shall be given on February 22, 1893.

"6. That in the event of any violation of any or all of the aforesaid stipulations, the said sum of $306,977 shall revert to me or such person or persons, institution or institutions as by testament or otherwise I may hereafter appoint. Such alteration of the preliminary medical course at present laid down in your University Register as shall leave undiminished the time required for preparation for that course, and the time required for the completion of that course, and the time devoted before and during that course to modern languages other than English, and to non-medical scientific studies, shall not be construed as violating the stipulations aforesaid."

These stipulations, and in particular those relating to the standard of admission, instruction and graduation in the Medical School, I make, not because of any misgiving in regard to the policy likely to be pursued by the present Board of Trustees, but because of the

obvious possibility that the policy might be altered by succeeding Trustees, and because of my own entire unwillingness to contribute at any time to the maintenance of an undergraduate or partly undergraduate school.

The sum of $306,977 thus offered to the Trustees of the University I propose to pay in yearly installments of $50,000 each, the first payment being made on January 1, 1894, and the last on January 1, 1899, adding to this final payment the additional sum of $6,977 still due; and in the meanwhile I will pay to the University in semi-annual payments interest at 5 per cent. per annum, computed from January 1, 1893, on such part of my gift as may remain from time to time in my hands, and I will, for the payment of all the said amounts, make such provision as will guarantee the University against all contingencies.

I am, very respectfully, yours,

MARY E. GARRETT.

ACTION OF UNIVERSITY TRUSTEES.

The following minute and resolution were adopted by the Trustees, December 24, 1892: "The President and Board of Trustees of the Johns Hopkins University having read and fully considered the generous offer made to them by Miss Mary Elizabeth Garrett, of Baltimore, in her letter of December 22, 1892, to place at their disposal the large sum of $306,977, in further endowment of the Medical School of the Johns Hopkins University, upon the conditions set forth in said letter, gratefully accept her offer and agree, for and on behalf of the said University, to perform fully all the conditions upon which her munificent gift is made.

"The money thus contributed shall be known and designated as the 'Mary Elizabeth Garrett Fund,' and a separate account thereof shall always be kept upon the books of the University.

"The committee named by her in her said letter shall be known to this Board as the 'Women's Committee of the Medical School,' and such committee shall be organized and always maintained in the manner set forth in her said letter, and shall perform the duties therein imposed upon it.

"The Baxley Fund, the Women's Medical School Fund and the fund now contributed by Miss Mary Elizabeth Garrett in aid of our Medical School will enable this Board to open such School in October, 1893. The School, when opened, will, we believe, because of its connection with the Johns Hopkins Hospital and because of the gifts which it has already received, and especially this last munificent gift, afford to the women and men of this country whose acquirements and training may enable them to enter upon its course of instruction, unsurpassed opportunities for the scientific study of medicine.

"*Resolved*, That the President of the Board of Trustees be requested to transmit to Miss Mary Elizabeth Garrett a copy of her letter, with a copy of this minute and resolution, under the seal of this University, and attested by him and by the Secretary thereof, annexed thereto, as a memorial of her liberality to this University and of its obligations to her."

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

Meeting of November 7, 1892—(continued).

Primary Tuberculosis of the Tonsil, Cheeks and Lips.—Dr. LORD.

This is a case of some interest, from the fact that the disease as it appears upon the face and the mucous membrane of the mouth resembles somewhat a syphiloderm. The history of the case is briefly as follows: Six years ago she had a fibroid tumor of the uterus and she consulted a physician, who placed her upon iodide of potash and mercury for the purpose of causing absorption of the growth. She has thus been for the past six years on the iodide and mercurials. After taking the iodides for three or four years an eruption appeared all over the body, resembling, as she states it, the small-pox. Two years ago an ulcer appeared on the right tonsil and an irregular soft small ulcer appeared on the inside of the left cheek. Half a year ago the ulcer spread to the upper lip, which became greatly swollen and extended down to the lower lip. We saw her a week ago for the first time, and our diagnosis lay between specific trouble and epithelioma. She was seen by three throat specialists and they thought it a cancer of the tonsil, which it resembles closely. The skin lesion looked like specific trouble. A section of skin was taken out and examined by Dr. Barker, who found it to be tuberculous. This variety of tuberculosis of the skin is exceedingly rare. In 4000 post mortems made by Chiari, only five cases of tuberculosis of the skin were found. These occurred in the regions where the mucous membrane and the skin come together, on the lips and about the anus, and in one case on the skin back of the ear. Any one might make a mistake in diagnosing such a case, and had we not made a microscopical examination and stained for the bacilli we could never have diagnosed it correctly. Upon the side of the right cheek there was a large patch resembling rupia, but upon removing the crust the lesion looks like tuberculosis.

The patient has had many of the symptoms of syphilis, rheumatic pains, falling out of hair, etc.

Progressive Muscular Dystrophy—Right Facial Paralysis.—Exhibition of Cases.—Dr. THOMAS.

Dr. Thomas presented a little girl to the Society who, he thought, was affected with progressive muscular dystrophy. He said the case was especially interesting, in being at a very early stage, where the diagnosis, although probable, could not be made with certainty. This is the sixth case of this affection he had the opportunity of showing to the Society.

The history was in short as follows: Girl four years old. Family history unimportant, no similar disease having occurred. She is the first child of three; the other two children are healthy. Her birth was normal and she appeared to be a strong baby. Mother noticed when she was very young that her eyes were crossed, and thinks that she has never seen as well as she should. She did not sit up until she was six months old, and she then had difficulty in holding up her head. She learned to walk clumsily at fifteen months; has improved somewhat, but has never been able to walk well. She has great difficulty in going up and down stairs. At present she seems a bright, fairly well-nourished child. The weakness in the muscles of the eye is evident. An ophthalmoscopic examination shows the optic nerves to be a little pale and that there is possibly some atrophy. As she stands, her head is bent somewhat forward, her back is arched, with the convexity in front, the abdomen is protruded; when the patient sits this deformity disappears. Her walk is "wobbly" and unsteady. She walks on her toes with the feet turned in. At every step her body is thrown over the foot that is on the ground. In getting up from the floor she has to help herself by putting her hands on her knees. There is neither marked atrophy nor hypertrophy of her muscles. The calf muscles are somewhat contracted and seem perhaps a little firmer than is usual. Nothing abnormal can be noticed about the shoulder-girdle or arms. She has not the "loose shoulders" that Erb considers so characteristic of this disease. A careful electrical examination has not as yet been made, and is difficult on account of the youth of the patient. However, both external

To Accompany Dr. Thomas's Case.

IN REPOSE.

STIMULATED BY FARADIC CURRENT.

popliteal nerves can be excited by a moderately strong faradic current, causing normal flexion of the feet.

In regard to diagnosis, Dr. Thomas said that the youth of the patient, her attitude when standing, her peculiar walk and her manner of getting up from the floor, all pointed to the case being one of progressive muscular dystrophy. On the other hand, the absence of any hypertrophy of the muscles and of the loose shoulders, and the presence of well-marked contractures of the calf muscles, make the case unusual and suggest the possibility that it may belong to the "peroneal type," called by Hoffman "progressive neurotic muscular atrophy." The electrical reactions seem to be normal, and this, too, favors the view that the case is one of progressive muscular dystrophy.

Dr. Thomas also presented a case in which there was, as far as he knew, a unique condition of a facial muscle. He showed the case in the hope that some of the members might be able to offer an explanation. The patient, girl, æt. 14, had inherited syphilis. She had scarlet fever as an infant, but was generally well until she was 4 years old, when she appeared to be drowsy and out of sorts for a few days, after which it was noticed that the right side of her face was paralyzed. Mother thinks that the paralysis was complete. Since then her face has somewhat improved. She came to the Dispensary a year ago and has been under observation ever since. The condition of the facial muscles has been practically unchanged during that time. At present, when face is at rest it is not easy to see which is the paralyzed side. The right side of face seems smaller and less well developed than the left. The right eye is more widely opened. When the patient is asked to elevate eyebrows and to close her eyes it is evident that the muscles on right side are much weaker than those on left. In endeavoring to show her upper teeth, the left upper lip is more elevated than the right. On the right there seems to be a good contraction of the levator labii superioris alæque nasi, unaccompanied by the other elevators. In stimulating the right facial nerve with the faradic current there is a weak contraction produced in those muscles which have voluntary power, except in the elevator of the nose and lip, which remains inactive. When the left facial is stimulated ½-inch in front of the ear, a point can be found which causes an isolated contraction of the right levator labii superioris alæque nasi. If the current be moderately strong, this is accompanied by a closure of the left eye. A strong current causes a contraction of all the muscles on left side of face, and this masks the contraction on the right. This muscle can also be stimulated when the electrode is placed on left side of nose, just below the inner angle of eye, and better still, in the analogous position on the right side. [*See accompanying plate.*]

In regard to the condition, Dr. Thomas said that he was at a loss for an explanation, but thought that it might be due to an abnormal distribution of the left facial nerve. He had been unable to find a report of a similar case.

A Case of Super-Secretion of the Gastric Juice.—Dr. THAYER.

The patient is a man forty years of age, who was admitted to the Hospital about two weeks ago. His trouble has lasted about two years. During all that time his complaint has been of severe periodical attacks of pain in the epigastrium, extending through into his back and radiating around on both sides. These attacks came on mainly during the night and when the stomach was empty. At times this pain was associated with the vomiting of large quantities of extremely acid and burning fluid. He complained also of sour, burning eructations and of considerable steady epigastric pain and soreness. His appetite was perfectly good, but he found that eating a general diet did not seem to "agree" with him, that his pains were worse afterwards, and consequently he restricted his diet very much. He lost much in weight; he weighed about 190 pounds when well, and on entrance his weight was but 125 or 130 pounds. Physical examination on entrance showed a man rather emaciated, complexion sallow, mucous membranes of fairly good color. Thoracic organs entirely negative. Abdomen flat; no abnormal masses to be felt on palpation; on inflating the stomach, however, we found that it was markedly dilated, extending some three or four finger-breadths below the umbilicus. The pylorus was not palpable. On the following morning the patient was given a test breakfast, consisting of one slice of bread (about 20 grammes) and one glass of water or a cup of tea without milk or sugar. Normally, after taking such a breakfast, if the tube is introduced an hour later one obtains about 20–40 cc. of slightly straw-colored cloudy fluid which gives a distinctly acid reaction to litmus paper, and deposits but a slight sediment. On testing further with Congo paper, which turns blue in the presence of a free acid, we should get evidence of a free acid, and that free acid should be found to consist largely of free hydrochloric acid (Günzburg's test). The starches in the ordinary process of digestion are so far changed in their way towards sugar that they should, under normal circumstances, give no reaction with Lugols' solution of iodine. The patient was given this test breakfast. He had nothing to eat during the night. On introducing the tube, nearly a quart of slightly cloudy fluid was obtained. There was a slight sediment. The fluid was intensely acid in reaction, and the test for free hydrochloric acid showed a markedly positive result. In the normal gastric juice the free acid present is almost entirely hydrochloric acid. The simplest clinical test is that for the total acidity, which is practically, under normal circumstances, the test for the quantity of hydrochloric acid. This is done by titration. One uses a decinormal solution of sodium hydrate in a burette, allowing it to fall drop by drop into 10 cc. of gastric juice (filtered). The acid of the normal gastric juice is such that it takes from 4—6—6.5 cc. of this solution to make alkaline 10 cc. of gastric juice, and one speaks shortly of a total acidity of one, three, four, six, etc. Above 6.5 one speaks of the gastric juice as being super-acid. The total acidity in this case was 11.3, that is, nearly twice the proportion of hydrochloric acid present under normal circumstances.

Last Sunday the patient's stomach was washed out with an alkaline solution and emptied. He was given nothing whatever during the night. Towards three or four o'clock in the morning he vomited quite a large quantity of fluid, and at about 8.30 or 9 o'clock in the morning the tube was introduced and 420 cc. of clear fluid secured, which had been secreted by the stomach during the night without any stimulation by the presence of food. This had an acidity of 11.7, even greater than we found at first.

This is one of those cases of super-secretion of the gastric juice associated, as it usually is, with super-acidity. One sees cases of the super-acidity of the gastric juice unassociated with super-secretion, that is, a condition where the normal call for acid which is given by an ordinary breakfast is answered by a secretion of gastric juice containing a greater amount of hydrochloric acid than is normally present, which appears sooner than it normally does and which produces distinct symptoms of pain, heartburn, etc. Then one sees cases of super-secretion, the great majority of which are associated with super-acidity. In Riegel's clinic, 19 out of 20 cases of super-secretion were associated with super-acidity.

Two years ago Dr. Osler had a patient in his practice whose gastric juice I had the opportunity to examine six or seven times. In that case, just as in this, quantities varying from half a pint to nearly a quart were obtained, the total acidity ranging from 9 to 13¼, even higher than it has been in this case.

If a continuous super-secretion of this kind is going on when the stomach is empty, the result after a certain length of time is a marked dilatation, and, in addition to the symptoms produced by super-acidity, one sees the symptoms of dilatation of the stomach.

It has been observed that it is in this class of cases one occasionally sees the so-called idiopathic muscular hypertrophies of the pylorus. Ewald thinks this is due to the spasmodic contraction of the pylorus as the result of irritation by the quantities of gastric juice in the stomach.

The treatment of these cases of super-secretion with super-acidity

is quite satisfactory. Of course one sees immediately that a stomach which is secreting the gastric juice so rich in its most important constituent can very easily digest albumen. In such cases the patient should be allowed albuminoids in quantity and albuminoids of almost any sort. It has been advised to give albuminoids of the grosser kinds,

Ewald says that pork is better than the more delicate albuminoids. The patient may be given considerable quantities of meat and egg-albumen. Fats are found to be fairly well borne, but it is better to give the simpler and more easily digested fats. Good butter is very well borne. The carbohydrates should be cut off as much as possible. Boas, in a very interesting article some years ago in the Berliner Med. Woch., laid great stress on the inadvisability of shutting off any one particular class of foods absolutely from the diet in ordinary diseases of the stomach, and I think this is a point which is often forgotten. If the patient is put on too strict a diet of one variety of food he becomes tired of it and rebels. We aim in this case to give the patient such a diet as his stomach will easily digest, which will at the same time use up as much of this super-acid gastric juice as is possible, and then again to give him a diet which will call for as little work as possible from the dilated stomach. We have tried to give him relatively small quantities of more solid food frequently during the day and to make that as albuminous as possible. He has four main meals in the day—at 8 A. M., 12 M., 4 and 8 P. M. At each meal he has meat, fish or eggs in moderate quantities. He is allowed a slice of toast or a cracker and good butter, and at two or three of these meals he is allowed a small cup of black coffee. Every two hours between meals he is given either a hard-boiled egg or a glass of milk, beef tea, beef juice, egg albumen or something of that sort, so that he gets something every two hours. He drinks only soda water, not more than 30 cc. at a time. He has borne his diet extremely well and has complained of no distress after eating since he has been in the Hospital. His stomach is washed out every morning with an alkaline solution of bicarbonate of soda and water. He has been given also small quantities of bicarbonate of soda every two hours while awake. He has two hard-boiled eggs placed by his bedside at night, and if he wakes up in the middle of the night with any pain he takes these eggs often with relief. The patient ha gained four or five pounds during the last ten days.

Rosenheim recommends in these cases the administration of nitrate of silver. It seems to relieve the pain somewhat and he thinks that it also tends to correct the super-acidity to some extent. He gives a grain of nitrate of silver in water three times a day on an empty stomach.

These conditions do not as a general thing yield very quickly to treatment; they last for years. The condition of the patient is, however, very greatly ameliorated. Dr. Osler's patient gained about thirty pounds under treatment, and the patient which we now have will go out in a day or two and be able to lead a comparatively comfortable life. In about a month he has gained 20 pounds.

This condition comes under the head of the gastric neuroses. It is more commonly found in hysterical and nervous individuals. It is interesting that the condition sometimes occurs periodically in hysterical individuals and at times in cases of tabes.

Dr. Hurd.—I remember seeing, a number of years ago, a patient who suffered in a similar manner, and his symptoms were largely relieved by eating the most indigestible sort of cheese. He formed the habit of eating cheese almost as frequently as Dr. Thayer's patient has formed the habit of eating other things. The Doctor's description of the number and variety of meals is very attractive, and I am sure that this disease cannot be wholly an evil.

Dr. Osler.—I would like to mention that I have seen the patient to whom Dr. Thayer refers within the past six or seven months, and he remains perfectly well. He came to me almost a skeleton. He was supposed to have malignant disease of the stomach, and had lost, I think, 50 or 60 pounds. Under Dr. Toulmin's management he recovered completely, and he has had no return of symptoms for fully two years, and has regained his weight and takes an ordinary diet.

Dr. Welch.—I would like to ask Dr. Thayer the condition of the urine.

Dr. Thayer.—Since entrance to the Hospital, no marked changes in the urine have been noted. In some cases of this nature a markedly diminished acidity has been described.

I should have said that cheese is also allowed at his four main meals.

Splenic Myelogenous Leukæmia—Exhibition of Patient.—Dr. Thayer.

I wish to speak briefly to-night of this case because the patient is soon to leave the Hospital.

The patient is a man 48 years of age, who first came to the Hospital on the 15th of October. He is a watchman, doing light work by day. He complained on entrance of fulness and distress after eating, with some nausea, and of a tumor on the left side of the abdomen. His family history is good and his personal history has no particular bearing on the present trouble. He had malaria three years ago; no chills since then. Habits good. Fifteen months ago he had an attack of what he calls influenza, and since that time he has not been wholly well. He has complained of vague dyspeptic symptoms and increasing weakness, and for two months dyspnœa on exertion. He noticed the tumor in his side two or three months ago. No hemorrhages; no priapism; eyesight perfectly good. On entrance his appearance was much the same as now, though somewhat paler. Examination of thoracic organs entirely negative. No œdema of any part. Abdomen found to be slightly prominent on left side. This was found to be due to a greatly enlarged spleen, reaching below and to the right of the umbilicus, and at the level of the umbilicus 7 cm. to the right of the median line. In the right margin, which was sharp, there were two or three distinct notches, a large one just above the umbilicus. The margin of the liver was not palpable, but apparently extended two or three finger-breadths below the costal margin. Examination of blood at that date showed no evidence of malarial organisms. Blood count gave 2,916,000 red corpuscles and 360,000 white corpuscles in the cubic millimeter. He had 47 per cent of hæmoglobin. Examination of dried and stained specimens of blood showed the characteristics of splenic myelogenous leukæmia. The patient was started immediately with Fowler's solution, three drops three times a day, and was told to increase the dose by one drop every fourth day. One week later there were 3,050,000 red corpuscles and 427,000 white corpuscles. Hæmoglobin slightly increased, 52 per cent. The next examination was made on November 2d, when he was taking 7 minims of Fowler's. Red corpuscles 3,547,000, white corpuscles 239,000, hæmoglobin 53 per cent. The count this afternoon shows red corpuscles 3,848,000, white corpuscles 256,000 to the cubic millimeter. Hæmoglobin 56 per cent.

(Exhibition and explanation of chart.)

I have under the microscopes several stained specimens of the patient's blood. They show very clearly the main characteristics of the blood in this form of leukæmia: (1) The great increase in the number of colorless corpuscles. (2) The number of the small mononuclear elements (lymphocytes) is greatly diminished. (3) In a blood showing extensive increase in the number of the leucocytes, the eosinophilic cells, that is, the leucocytes with coarse granules which stain only with acid coloring matters, are present in about the normal relative proportions, whereas in most leucocytoses the eosinophilic cells take no part in the increase and are present in greatly reduced proportion. (4) A distinct number of very large leucocytes, larger than any we ordinarily see, containing a single nucleus and having in their protoplasm granules stained by neutral coloring matters. (5) We also find a considerable number of nucleated red corpuscles. (6) Another striking point is the great difference in size between different polynuclear cells as well as with the eosinophils.

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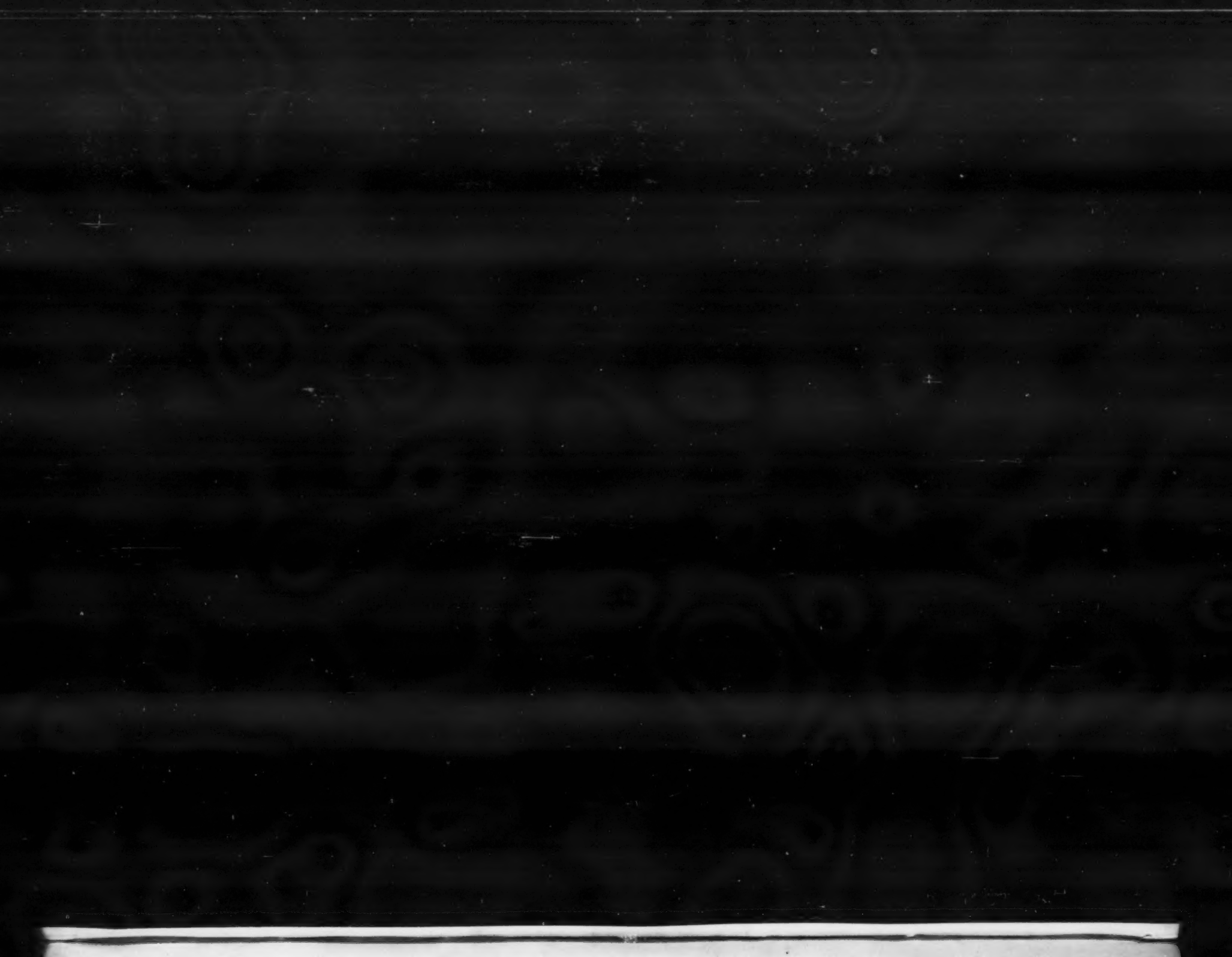
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